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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,599	NOLAN ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-33,35-42 and 44-70* is/are pending in the application.

4a) Of the above claim(s) *35,36 and 46-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33,37-42,44,45 and 67-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 10/01/04 in response to the non-final Office Action mailed 07/30/04.

Status of Claims

2) Claims 31, 32, 37, 45, 67, 68 and 70 have been amended via the amendment filed 10/01/04.

Claim 43 has been canceled via the amendment filed 10/01/04.

Claims 30-33, 35-42 and 44-70 are pending.

Claims 30-33, 37-42, 44, 45 and 67-70 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

5) The rejection of claim 43 made in paragraph 11 of the Office Action mailed 07/30/04 under 35 U.S.C § 112, first paragraph, as being as new subject matter, is moot in light of Applicants' cancellation of the claim.

6) The rejection of claim 43 made in paragraph 12(a) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 43 made in paragraph 12(f) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

8) The rejection of claim 43 made in paragraph 13 of the Office Action mailed 07/30/04 under 35 U.S.C § 102(b) as being anticipated by Barondess *et al.* (*Nature* 344: 871-874, 1990,

already of record) (Barondess, 1990) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, already of record), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

9) The rejection of claim 37 made in paragraph 12(b) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 68 made in paragraph 12(c) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claims 31 and 32 made in paragraph 12(d) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

12) The rejection of claim 45 made in paragraph 12(e) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claims 38-42, 44, 45 and 67 made in paragraph 12(f) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

14) The rejection of claims 37-40, 67 and 68 made in paragraph 13 of the Office Action mailed 07/30/04 under 35 U.S.C § 102(b) as being anticipated by Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess, 1990) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, already of record), is withdrawn. A new ground of rejection(s) is made herebelow. The following statements of Applicants made in the paragraph bridging pages 9 and 10 of Applicants' amendment filed 10/01/04 in response to this art rejection have been noted:

> Independent claims 37 and 68 each recite an "immunogenic composition". The specification defines "immunogenic composition" as referring "to a composition or preparation administered in an amount effective to raise antibodies in a recipient and *further provides some therapeutic benefit or effect s as to result in an immune response that inhibits or prevents a septicemic disease in a subject*, or so as to result in the production of antibodies to a virulent complement resistant avian *E. coli* isolate, or polypeptide or peptide employed as an immunogen." Specification at page 43, lines 19-24, emphasis added. Thus, independent claims 37 and 68 are directed to compositions that, inter alia, provide "some therapeutic

benefit or effect so as to result in an immune response that inhibits or prevents a septicemic disease in a subject." [Emphasis in original].

15) The rejection of claims 37 and 41 made in paragraph 14 of the Office Action mailed 07/30/04 under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess *et al.*, 1990) in view of Applicants' admitted state of the prior art, is withdrawn. A new ground of rejection(s) is made herebelow.

16) The rejection of claim 42 made in paragraph 15 of the Office Action mailed 07/30/04 under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess *et al.*, 1990) and Krieg *et al.* (WO 96/02555, already of record), is withdrawn. A new ground of rejection(s) is made herebelow.

Rejection(s) Maintained

17) The rejection of claim 70 made in paragraph 11 of the Office Action mailed 07/30/04 under 35 U.S.C § 112, first paragraph, as being as new subject matter, is maintained for reasons set forth therein.

Applicants submit that they have amended the claim to remove the second recitation of 'or an immunogneic subunit or immunogenic fragment thereof'. However, the claim still includes at least such recitation. The rejection stands.

18) The rejection of claim 70 made in paragraph 12(a) of the Office Action mailed 07/30/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

Applicants submit that they have amended the claim to remove the second recitation of 'or an immunogenic subunit or immunogenic fragment thereof'. However, the claim still includes at least such recitation. The rejection stands.

Rejection(s) under 35 U.S.C § 112, First Paragraph

19) Claims 37-42, 44, 45 and 67-70 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide encoding an avian *E. coli* Iss polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or an immunogenic fragment or immunogenic subunit of the polypeptide, does not reasonably provide enablement for an 'immunogenic composition' comprising an isolated nucleic acid molecule comprising a

nucleotide sequence encoding an avian *E. coli* Iss polypeptide or an immunogenic fragment or immunogenic subunit of the polypeptide as claimed in the independent claim 37 or 68, and for an 'immunogenic composition' comprising an isolated nucleic acid molecule comprising a nucleotide sequence comprising nucleotides 73 to 309 of the nucleotide sequence of SEQ ID NO: 22 as claimed in claim 69 or 70. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to an 'immunogenic composition' comprising a nucleic acid molecule, i.e., a DNA vaccine. With regard to the required characteristics of this nucleic acid-containing 'immunogenic composition', Applicants point to page 43, lines 19-24 of the instant specification and make the following statements (see the paragraph bridging pages 9 and 10 of Applicants' amendment filed 10/01/04):

> Independent claims 37 and 68 each recite an "immunogenic composition". The specification defines "immunogenic composition" as referring "to a composition or preparation administered in an amount effective to raise antibodies in a recipient and *further provides some therapeutic benefit or effect s as to result in an immune response that inhibits or prevents a septicemic disease in a subject*, or so as to result in the production of antibodies to a virulent complement resistant avian *E. coli* isolate, or polypeptide or peptide employed as an immunogen." Specification at page 43, lines 19-24, emphasis added. Thus, independent claims 37 and 68 are directed to compositions that, inter alia, provide "some therapeutic benefit or effect so as to result in an immune response that inhibits or prevents a septicemic disease in a subject." [Emphasis in original].

With this and throughout the page 10 and a part of page 11 of the amendment filed 10/01/04, Applicants insist that the claimed nucleic acid composition, as defined in the instant specification, is **required** to provide some 'therapeutic benefit or effect' so as to result in an

immune response that 'inhibits or prevents a septicemic disease in a subject'. An analysis of the instant claims indicates the following. The isolated nucleic acid molecule recited in claims 68-70 comprising the recited nucleotide sequence is not required to be associated with a host promoter or non-host promoter, whereas the isolated nucleic acid molecule recited in the independent claim 37 comprises at least one regulatory sequence or control sequence operably linked to the nucleotide sequence encoding the polypeptide. Only the nucleic acid molecule recited in the dependent claim 41 is required to have a regulatory or control sequence that causes expression of the polypeptide in an animal cell. A review of the instant specification indicates the following. The specification at page 47, for example, states that the nucleic acid molecule can be supplied as part of a vector or as a 'naked' nucleic acid molecule. However, it is unlikely that the nucleic acid molecule alone as claimed in some of the claims, i.e., naked DNA, without an appropriate promoter, would express an Iss polypeptide or an immunogenic fragment or subunit of the polypeptide in any host. There is absolutely no evidence within the instant specification that the naked nucleic acid molecule as recited somehow got expressed, with or without a host promoter, *in vivo* in an avian or mammalian subject to produce an Iss polypeptide, or an immunogenic fragment or subunit thereof, which induced 'some therapeutic benefit or effect so as to result in an immune response that inhibits or prevents a septicemic disease' in the avian or mammalian subject. There are no methods or working examples disclosed in the instant application whereby the recited nucleic acid molecule is demonstrated to be expressed *in vivo* in an avian or mammalian host thus encoding *in vivo* the full length Iss polypeptide or an immunogenic fragment or subunit thereof in the host wherein polypeptide, subunit or fragment thereof 'prevented' or 'inhibited' septicemic disease in the host by a virulent complement resistant avian *E. coli* isolate. No part of the instant specification establishes that the recited *Iss* nucleic acid molecule or the one comprising nucleotides 73 to 309 of the nucleotide sequence of SEQ ID NO: 22, with or without nucleotides 1 to 33 of the nucleotide sequence of SEQ ID NO: 21 and with or without an immunostimulatory nucleotide sequence, was indeed made which was able to induce some therapeutic benefit or effect so as to result in an immune response that 'inhibited' or 'prevented' a septicemic disease in an avian or mammalian subject to whom it was administered as a composition. The specification at page 47 of the instant specification states

that general methods for construction, production and administration of nucleic acid molecule vaccines are known in the art. However, the specification does not teach any methods or working examples showing that an *E. coli* Iss nucleic acid molecule as recited is introduced and expressed in a host for therapeutic or prophylactic purposes. The disclosure in the specification is merely an invitation to an artisan to use the current invention as a starting point for further experimentation. The 'prevention' of a septicemic disease in an avian or mammalian host by administration of an immunogenic composition comprising the isolated nucleic acid molecule as recited in the instant claims is highly complex and unpredictable. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (see abstract of Phillips, A. *J Pharm Pharmacology* 53: 1169-1174, 2001). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (see paragraph 1 on page 1170 of Phillips, A., 2001). Phillips also states that the problem with gene therapy is two-fold: (a) a system must be designed to deliver DNA to a specific target and to prevent degradation within the body, and (b) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (see paragraph 1 on page 1170 of Phillips, A., 2001). Thus, gene therapy is unpredictable and complex wherein one of skill in the art may not necessarily be able to introduce and express an *Iss* nucleic acid or a part thereof in the cells of an avian or mammalian host, or be able to produce the Iss polypeptide, an immunogenic fragment or subunit thereof in that host such that the polypeptide, or immunogenic fragment or subunit thereof 'prevents' or 'inhibits' septicemic disease due to a virulent complement resistant avian *E. coli* isolate in that host. The *Webster's II New Riverside University Dictionary* (1984) defines the term 'prevent' as 'to keep from happening'. Infection due to a virulent complement resistant avian *E. coli* isolate encompasses microbial cell invasion and growth or multiplication of the virulent bacterial isolate therein. The term 'infect' is defined in the illustrated *Stedman's Medical Dictionary* (24th Edition, 1982) as 'to enter, invade, inhabit, or to dwell internally'. The specification does not enable an Iss nucleic acid-containing composition which keeps the process of *E. coli* septicemic infection from

happening, or which 'prevents' the entry and invasion of a virulent complement resistant avian *E. coli* into a cell or its internal dwelling on administration of the claimed nucleic acid-containing immunogenic composition of the instant invention to a subject or patient. Therefore, due to the lack of direction/guidance and lack of enabling working examples in the instant specification, the complex nature of the invention, the lack of evidentiary support in the specification enabling the claimed nucleic acid-containing composition as a therapeutic or prophylactic composition, the unpredictability known in the art of transferring genes into host's cells such that therapeutic or prophylactic levels of a polypeptide, subunit or fragment thereof are expressed *in vivo* in the host so as to prevent or inhibit septicemia in the host, the breadth of the claims, and the large quantity of experimentation necessary, undue experimentation would have be required by one of skill in the art to make and use the invention or to reproducibly practice the invention as claimed. The production and use of an *Iss* nucleic acid-containing composition that is capable of inducing any therapeutic effect which 'prevents' or 'inhibits' septicemic disease in an animal is well outside the realm of routine experimentation. The claims are viewed as not meeting the enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

20) Claims 37-42, 44, 45, 67 and 68 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 37 is vague and confusing in the limitation 'the polypeptide' (see line 4 and 6) because it is unclear which of the two polypeptides recited in line 3 of the claim provides antecedence to this limitation: 'Iss polypeptide' or 'a polypeptide comprising ….. Iss polypeptide'?

(a) Claim 68 is vague and confusing in the limitation 'the polypeptide' (see line 4) because it is unclear which of the two polypeptides recited in line 3 of the claim provides antecedence to this limitation: 'Iss polypeptide' or 'a polypeptide comprising ….. Iss polypeptide'?

(b) Claim 41, dependent from claim 37, is vague and confusing in the limitation 'the polypeptide' (see line 2) because it is unclear which of the two polypeptides recited in claim 37

provides antecedence to this limitation.

(c) Analogous criticism applied to claim 67.

(d) Claim 67 is confusing and/or lacks antecedent basis in the limitations 'subunit' or 'fragment' (see lines 2 and 3). Claim 44, depends indirectly from claim 37, which recites 'an immunogenic fragment' and 'an immunogenic subunit of the polypeptide'. Is the 'subunit' or 'fragment' recited in claim 67 non-immunogenic?

(e) Claims 38-42, 44, 45 and 67, which depend directly or indirectly from 37, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Objection(s)

21) Claims 30-33, 44, 45, 69 and 70 are objected for the incorrect recitation: 'sequence SEQ ID NO: 22' and/or 'sequence SEQ ID NO: 21' as opposed to the recitation --sequence of SEQ ID NO: 22-- and/or --sequence of SEQ ID NO: 21--.

Remarks

22) Claims 37-42, 44, 45 and 67-70 stand rejected. Claims 30-33 contain allowable subject matter.

23) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

24) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

25) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be

reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

January, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER